UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/519,417	12/22/2004	Patrick Cornelis Nicolaas Rensen	101137-60	7547

27387 7590 09/13/2010

LONDA, BRUCE S.
NORRIS MCLAUGHLIN & MARCUS, PA
875 THIRD AVE, 8TH FLOOR
NEW YORK, NY 10022

EXAMINER	
HINES, JANA A	

ART UNIT	PAPER NUMBER
1645	

MAIL DATE	DELIVERY MODE
09/13/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/519,417	RENSEN ET AL.	
	Examiner	Art Unit	
	JaNa Hines	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 August 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17-20 and 22-34* is/are pending in the application.

4a) Of the above claim(s) *19,20,29 and 33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17, 18, 22-28, 30-32 and 34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 16, 2010 has been entered.

Claim Status

2. Claims 1-16 and 21 are cancelled. Claims 19-20, 29 and 33 are withdrawn from consideration. Claims 17, 22-28, 30-32 and 34 are under considerations in this office action.

Response to Arguments

3. Applicant's arguments filed May 18, 2010 and August 16, 2010 have been fully considered but they are not persuasive.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 17-18, 22-28, 30-32 and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dasseux et al., (WO 99/16458 published April 8, 1999) in view of Rozek et al., (Biochemistry. 1995. Vol. 34, pages 7401-7408).

The claims are drawn to a method for treating a mammal suffering from or is at risk of developing sepsis or septic shock comprising administering to such mammal a therapeutically effective amount of a peptide and pharmaceutically acceptably adjuvants where the peptide comprises an amino acid sequence selected from SEQ ID NO:11, SEQ ID NO:2 and SEQ ID NO:1.

Dasseux et al, teach apolipoprotein A-1 agonist compositions for treating septic shock (page 1, lines 5-9). Dasseux et al, teach the desire to mimic the activity ApoA-I with specific activities such as activation of LCAT approaching that of the native molecule (page 17, lines 17-21). Dasseux et al, teach the ApoA-I agonist are peptides that form amphipathic helices in the presence of lipids, bind lipids, form pre-B-like or HDL-like complexes, activate LCAT, increase serum levels of HDL fractions and promote cholesterol efflux (page 17, lines 20-27). Dasseux et al, teach the peptide design is based on the helical structure and amphipathic properties of 22 amino acid consensus sequence derived from the helical repeats of ApoA-I (page 17, lines 28-32). Dasseux et al, teach the having negative charges being distributed on the rest of the hydrophilic face of the peptide (page 33, lines 25-29). Dasseux et al, the agonist can be used to treat any animals, especially mammals, including humans for enotoxemia which results in septic shock (page 78, lines 9-20). It is noted that sources of sepsis or septic

shock can be caused by gram-negative or gram-positive bacteria. Dasseux et al, teach administering the peptide by any suitable route to ensure bioavailability (page 83, lines 30-36) and pharmaceutical formulations including a wide variety of pharmaceutically acceptable adjuvant carriers (page 76, lines 24-32). However Dasseux et al, do not teach administering SEQ ID NO:1, 2 or 11.

Rozek et al., teach apolipoprotein C-I (ApoC-I) is an exchangeable apolipoprotein distributed mainly in HDL and VLDL, where HDL facilitates the uptakes of cholesterol (page 1858, col.1). Rozek et al., teach that LCAT is primarily activated by ApoA-I, whereas ApoC-I serves as the secondary activator and stimulates LCAT activity up to 78% as effectively as ApoA-I (page 1858, col.2). Rozek et al., teach ApoA-I having affinity for lipids (page 1859, col.1). The main structural motif which facilitates the interaction of the exchangeable apolipoprotein with lipids is the amiphipathic helix which is defined as an a-helix with opposing polar and nonpolar faces (page 1859, col.1). Rozek et al., notes that Rozek et al., (Biochemistry 1995, Vol. 34:7401-7408) disclose peptides corresponding to the lipid binding domain of ApoC-I and is characterized by repeating amino acid motifs of 22 resides which form the amphipathic helical structure when associated with lipids (Rozek et al., (Biochemistry 1995, Vol. 34:7401). Furthermore ApoC-I directly increases HDL serum levels. Rozek et al., teach the hydrophobic side chains are exclusively on the concave face, forming two hydrophobic clusters; there are positively charged side chains at the interface of the peptide and the negatively charged side chains are located on the hydrophilic face of the molecules

(page 1863-4, col.2-2). Furthermore, Rozek et al., disclose peptides comprising amino acid sequences from SEQ ID NO:11, 2 and 1.

Therefore it would have been prima facie obvious at the time of applicants' invention to apply the peptide comprising the amino acid sequence as taught by Rozek et al., into the method for treating a mammal suffering from or is at risk of developing sepsis or septic shock comprising administering a therapeutically effectively amount of a peptide and pharmaceutically acceptably adjuvants as taught by Dasseux et al., in order to provide an apolipoprotein A-I composition for treating endotoxemia or septic shock. One of ordinary skill in the art would have a reasonable expectation of success by including ApoC-I peptide within the composition of method of treating sepsis or shock because the art teaches the using peptides that mimic the activity ApoA-I such as activators of LCAT and Rozek et al., teach the ApoC-I peptide has said activation ability. Furthermore, no more than routine skill would have been required to include the ApoC-I peptide because Rozek et al., teach that the ApoC-I peptide forms amphipathic helices in the presence of lipids, bind lipids with its lipid binding domains, increases serum levels of HDL fractions and promotes cholesterol efflux, just as required of an ApoA-I agonist taught by Dasseux et al. Finally all of the claimed elements, such as the peptides qualify as ApoA-1 agonist and peptides comprising SEQ ID NO:1, 2, or 11, were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

Claim Rejections - 35 USC § 103

5. Claims 17-18, 22-28, 30-32 and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dasseux et al., (US Patent 6,004,925 published December 21, 1999) in view of Rozek et al., (Biochemistry. 1995. Vol. 34, pages 7401-7408).

The claims are drawn to a method for treating a mammal suffering from or is at risk of developing sepsis or septic shock comprising administering to such mammal a therapeutically effective amount of a peptide and pharmaceutically acceptably adjuvants where the peptide comprises an amino acid sequence selected from SEQ ID NO:11, SEQ ID NO:2 and SEQ ID NO:1.

Dasseux et al, teach apolipoprotein A-1 agonist compositions for treating disorders such as septic shock (col. 2, lines 55-5). Dasseux et al, teach the desire to mimic the activity ApoA-I with specific activities such as activation of LCAT approaching that of the native molecule (col. 11, lines 50-55). Dasseux et al, teach the ApoA-I agonist are peptides that form amphipathic helices in the presence of lipids, bind lipids, form pre-B-like or HDL-like complexes, activate LCAT, increase serum levels of HDL fractions and promote cholesterol efflux (col. 11, lines 55-60). Dasseux et al, teach the peptide design is based on the helical structure and amphipathic properties of 22 amino acid consensus sequence derived from the helical repeats of ApoA-I (col.11, lines 61-67). Dasseux et al, teach the having negative charges being distributed on the rest of the hydrophilic face of the peptide (col. 20, lines 48-53). Dasseux et al., teach pharmaceutical formulations containing ApoA-I agonist and their use to treat diseases associated with endotoxemia, i.e., septic shock (col. 12, lines 14-21).Dasseux et al, the

agonist can be used to treat any animals, especially mammals, including humans for enotoxemia which results in septic shock (col. 49, lines 47-59). It is noted that sources of sepsis or septic shock can be caused by gram-negative or gram-positive bacteria. Dasseux et al, teach administering the peptide by any suitable route to ensure bioavailability (col. 52, lines 46-67) and pharmaceutical formulations including a wide variety of pharmaceutically acceptable adjuvant carriers (col. 48, lines 59-68). However Dasseux et al, do not teach administering SEQ ID NO:1, 2 or 11.

Rozek et al., teach apolipoprotein C-I (ApoC-I) is an exchangeable apolipoprotein distributed mainly in HDL and VLDL, where HDL facilitates the uptakes of cholesterol (page 1858, col.1). Rozek et al., teach that LCAT is primarily activated by ApoA-I, whereas ApoC-I serves as the secondary activator and stimulates LCAT activity up to 78% as effectively as ApoA-I (page 1858, col.2). Rozek et al., teach ApoA-I having affinity for lipids (page 1859, col.1). The main structural motif which facilitates the interaction of the exchangeable apolipoprotein with lipids is the amiphipathic helix which is defined as an a-helix with opposing polar and nonpolar faces (page 1859, col.1). Rozek et al., notes that Rozek et al., (Biochemistry 1995, Vol. 34:7401-7408) disclose peptides corresponding to the lipid binding domain of ApoC-I and is characterized by repeating amino acid motifs of 22 resides which form the amphipathic helical structure when associated with lipids (Rozek et al., (Biochemistry 1995, Vol. 34:7401). Furthermore ApoC-I directly increases HDL serum levels. Rozek et al., teach the hydrophobic side chains are exclusively on the concave face, forming two hydrophobic clusters; there are positively charged side chains at the interface of the peptide and the

negatively charged side chains are located on the hydrophilic face of the molecules (page 1863-4, col.2-2). Furthermore, Rozek et al., disclose peptides comprising amino acid sequences from SEQ ID NO:11, 2 and 1.

Therefore it would have been prima facie obvious at the time of applicants' invention to apply the peptide comprising the amino acid sequence as taught by Rozek et al., into the method for treating a mammal suffering from or is at risk of developing sepsis or septic shock comprising administering a therapeutically effectively amount of a peptide and pharmaceutically acceptably adjuvants as taught by Dasseux et al., in order to provide an apolipoprotein A-I agonist composition for treating endotoxemia or septic shock. One of ordinary skill in the art would have a reasonable expectation of success by including ApoC-I peptide within the composition of method of treating sepsis or shock because Dasseux et al, teach the using peptides that mimic the activity ApoA-I such as activation of LCAT and Rozek et al., teach the ApoC-I peptide has said ability. Furthermore, no more than routine skill would have been required to include the ApoC-I peptide because Rozek et al., teach that the ApoC-I peptide forms amphipathic helices in the presence of lipids, bind lipids with its lipid binding domains, increases serum levels of HDL fractions and promotes cholesterol efflux, just as required of an ApoA-I agonist as taught by Dasseux et al. Finally all of the claimed elements, such as peptides that qualify as ApoA-1 agonist and peptides comprising SEQ ID NO:1, 2, or 11, were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions and the

combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

Response to Arguments

6. Applicant's arguments filed August 16, 2010 have been fully considered but they are not persuasive. It is noted that the response argues both the 103 together in view the rejections use of similar art; therefore the response will address the arguments in kind.

Applicants assert that the structures involved in LPS binding in ApoC(1), ApoE(2) and ApoA1 are not necessarily equal to their lipid binding helical structures. However Applicants mere arguments without any scientific evidence to support such a position is not persuasive. Contrary to applicants assertion, the prior art teaches the related functions of the apolipoproteins along with peptide design similarities. Dasseux et al, teach the desire to mimic the activity ApoA-I with specific activities such as activation of LCAT approaching that of the native molecule. Dasseux et al, teach the ApoA-I agonist are peptides that form amphipathic helices in the presence of lipids, bind lipids, form pre-B-like or HDL-like complexes, activate LCAT, increase serum levels of HDL fractions and promote cholesterol efflux. Rozek et al., disclose ApoC-I peptides corresponding to the lipid binding domain of ApoC-I and are characterized by repeating amino acid motifs which form the amphipathic helical structure when associated with lipids; thereby meeting the requirements of Dasseux et al., ApoA-1 agonist; which provides motivation for combining the references.

Applicants assert "..that not all peptides based on apolipoproteins do bind LPS and lipid binding and LPS binding are mediated by different structural elements, of which the LPS binding elements are only present in some apolipoproteins and when present can be structurally very different between apolipoproteins..." In response to applicant's argument, the examiner's conclusion is not based upon the similarities of ApoA-I and ApoC-I; rather the Examiner's reasoning is based upon the teachings of Dasseux et al., who use ApoA-I agonist for treating sepsis, and teach specific structural qualities need by peptides to be useful peptides within the method of treating along with the prior art teachings that Rozek et al., which teach peptides encompassing the structural requirements and having the needed abilities to meet the qualifications for being ApoA-I agonist. The issue is not that all apolipoproteins bind by the exact same mechanism or have the exact same structure; rather the issue is that the apolipoproteins of Rozek et al., meet the limitations taught by Dassuex et al.

Therefore applicants arguments about the differences and general conclusions about ApoA-I and ApoC-I are not persuasive since the rejection is on the grounds that all of the claimed elements, such as the peptides qualifying as ApoA-1 agonist and peptides comprising SEQ ID NO:1, 2, or 11, were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

Applicants assert that it is not possible to predict the LPS binding and the effect on sepsis of ApoC1 from structural and functional properties of ApoA1. However

Applicant is remind that there is no requirement for such. In this case, the examiner's conclusion is not based upon the similarities of ApoA-I and ApoC-I; rather the Examiner's reasoning is based upon the teachings of Dasseux et al., use of ApoA-I agonist for treating sepsis, along with Dasseux et al., teaching of specific structural qualities need by peptides to be useful peptides and the prior art teachings that Rozek et al., teach peptides encompassing the structural requirements and having the needed abilities to meet the qualifications for being ApoA-I agonist.

Applicants urges that it is interesting that the effects of ApoA1, ApoE and ApoC1 re very different. However this observation is not persuasive. It is noted that the observed differences upon which applicant relies are not recited in the rejected claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Finally, applicants assert that the assumption that any ApoA-I agonist, where the agonist activity would be structurally related, would have the desired therapeutic effects, fails because of the inherent variability of structurally related activity of the apolipoproteins. However, arguments about the differing structural similarities and differences as argued by applicants is not persuasive, since the rejection is based on peptides which act as ApoA-I agonist, not about the differences between ApoA-I, AopE and ApoC-I. Accordingly, the arguments about the size difference between the apolipoproteins are not persuasive in view of the art teachings. Moreover, applicants arguments about the differences between ApoA-I and ApoC-I are not persuasive since

the rejection is on the grounds that all of the claimed elements, such as the peptides qualifying as ApoA-1 agonist and peptides comprising SEQ ID NO:1, 2, or 11, were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

Therefore applicants' arguments and observations are not found persuasive and the rejection is maintained.

Conclusion

7. No claims allowed.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ja-Na Hines whose telephone number is 571-272-0859. The examiner can normally be reached Monday thru Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Larry Helms, can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/JaNa Hines/
Examiner, Art Unit 1645

/Mark Navarro/

Primary Examiner, Art Unit 1645